| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/752,639 | GATANAGA ET AL. | |
| | Examiner | Art Unit | |
| | Joseph F Murphy | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *33-58* is/are pending in the application.

4a) Of the above claim(s) *34,41-44,46-50 and 52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33, 35-40, 45, 51, 53-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Formal Matters*

Claims 33, 35, 57-58 were amended in Paper No. 12, 3/24/2003. Claims 33-58 are pending. Claims 34, 41-44, 46-50, 52 stand withdrawn from consideration pursuant to 37 CFR 1.142(b). Claims 33, 35-40, 45, 51, 53-58 are under consideration.

### *Election/Restrictions*

In Paper No. 8, 6/24/2002 Applicant elected with traverse of Group IX, claims 33-34 as drawn to a method of screening a substance for an ability to affect TRRE activity, wherein the polypeptide has the sequence of SEQ ID NO: 9. The traversal was on the grounds that there would be no burden to search methods using the other polypeptides. This was not found persuasive, and the requirement was deemed proper and made FINAL in Paper No. 10, 9/26/2003. Each application before the office is examined on its own merits. Should Applicant desire consideration of the final restriction in the instant application, the applicant, in addition to making any reply due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal.

### *Response to Amendment and Arguments*

Applicant's arguments filed in Paper No. 12, 3/24/2003 have been fully considered but they are persuasive in part or the reasons set forth below. Additionally, new issues are set forth below.

The objection to the Specification has been withdrawn.

The rejection of claims 33 and 35 under 35 USC 112 second paragraph has been withdrawn based on Applicant's amendment.

***Claim Objections***

Claims 35, 39 and 40 stand objected to because of the following informalities: They contain limitations drawn to non-elected inventions. Appropriate correction is required. The objection will not be held in abeyance since each application is examined on its own merits.

***Claim Rejections - 35 USC § 112 first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35, 39, 40, 45, 51 stand rejected, and claims 33, 36-38, 53-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening substances for an ability to affect the TRRE activity of the protein encoded by SEQ ID NO: 9, does not reasonably provide enablement for a method of screening substances for an ability to affect the TRRE activity of the protein encoded by a fragment of the longest open reading frame of SEQ ID NO: 9, or a method of screening substances for an ability to affect the TRRE activity of the protein encoded by a polynucleotide that hybridizes to a nucleic acid that encodes SEQ ID NO: 9, for reasons of record as set forth in paper No. 10, 9/26/2003, and for additional reasons set forth below. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The rejection of record set forth that claims 35, 39, 40, 45, 51 are overly broad since no guidance is provided as to which of the myriad of polypeptide species encompassed by the claim will retain the characteristics the polypeptide encoded by SEQ ID NO: 9. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of TRRE. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). Since the claims encompass methods using muteins of TRRE, and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to practice the claimed method.

Applicant argues that the Office has not established a prima facie case for lack of enablement because the Specification provides assays that can identify variant polypeptides with TRRE activity. Applicant further argues that polypeptide variants with TRRE activity may be produced by routine experimentation, and identified by the screening assays set forth in the Specification. However, claims 35, 39, 40, 45, 51 are drawn to screening methods using a polypeptide encoded by the longest open reading frame of a nucleic acid, or a fragment of such a

polypeptide. Since detailed information regarding the structural and functional requirements of the encoded polypeptide is lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant argues that the specification sets forth that polypeptide variants of TRRE can be constructed and then tested for functionality, then used in the claimed method. However, Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass methods using polypeptides which the specification only teaches one skilled in the art to test for functional variants to be used in the claimed method. It would require undue experimentation for one of skill in the art to practice the claimed method, since the skilled artisan would have to first make polypeptide variants of TRRE, then test for function. Because the amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex, accurate predictions of a polypeptide's structure from mere sequence data are limited. Thus, since Applicant has only taught how to test for polypeptide variants of TRRE, and has not taught how to make polypeptide variants of TRRE, it would require undue experimentation of one of skill in the art to practice the claimed method.

Applicant additionally argues that the Office has a policy of allowing closely related sequences, and cites a recently issued patent. However, each Application is examined on its own merits, and consideration of unrelated applications which have issued is beyond the scope of this Action.

Additionally, claim 33, and dependent claims 36-38, 53-58 are overly broad because they define a polypeptide used in the method by a function alone, i.e. the polypeptide causes TNF receptor to be cleaved. However, in Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d

1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. In the instant case, there are no structural features set forth for the polypeptide that must have the function of cleaving TNF receptor, thus it would require undue experimentation for one of skill in the art to determine which polypeptides, given no structural information, would retain the function of cleaving TNF receptor.

Given the breadth of claims 33, 35-40, 45, 51, 53-58 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to practice the claimed invention.

Claims 35, 39, 40, 45, 51 stand rejected, and claims 33, 36-38, 53-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record as set forth in paper No. 10, 9/26/2003, and for additional reasons set forth

below. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

These are genus claims. According to the specification, the term variant means a protein having one or more amino acid substitutions, deletions, insertions and/or additions made to the polypeptide encoded by SEQ ID NO: 9. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the polypeptide encoded by SEQ ID NO: 9. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the specification states that these types of changes are routinely done in the art, the specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the polypeptide encoded by SEQ ID NO: 9 alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Applicant argues that the claims as presented meet the Written Description standard as set forth in the written description guidelines. However, claims 35, 39, 40, 45, 51 are drawn to screening methods using a polypeptide encoded by the longest open reading frame of a nucleic acid, or a fragment of such a polypeptide. Applicant argues that the Written Description Guidelines indicate that polynucleotide sequences claimed according to their ability to hybridize to a representative sequence fall within the written description requirements of 35 USC 112 first paragraph. However, in the example in the Written Description Guidelines (Example 9) the claim covers full length polynucleotides which hybridize to SEQ ID NO: 1, and there is also a functional limitation wherein the encoded protein must bind dopamine and stimulate adenylate cyclase. In the instant case, the claims are drawn to methods which use polypeptides which are encoded by fragments of a nucleic acid. However, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides used in the claimed method. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the

compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed: there is no guidance in the art as to what the defining characteristics of the polypeptides might be. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the molecules which would function in the claimed method.

Additionally, claim 33, and dependent claims 36-38, 53-58 lack written description because they define a polypeptide used in the method by a by a function alone, i.e. the polypeptide causes TNF receptor to be cleaved. However, in University of California v. Eli Lilly, 119 F.3 at 1568, 43 USPQ2d at 1406. the Court decided that a definition by function alone "does not suffice" to sufficiently describe a biomolecule "because it is only an indication of what the gene does, rather than what it is." Further, "it is only a definition of a useful result rather that a definition of what achieves that result...The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention". *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). While Applicant has set forth a method for obtaining a polypeptide which causes TNF receptor to be cleaved, Applicant has not set forth within the

claim the detailed constitution of the this polypeptide, and thus does not satisfy the written description requirement.

***Claim Rejections - 35 USC § 112 second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40 and 51 stand rejected, and claims 33-39, 45, 53-58 are rejected, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record as set forth in paper No. 10, 9/26/2003.

Claims 40 and 51 recite the term "stringent conditions", which is a conditional term and renders the claim indefinite. Furthermore, some nucleic acids that might hybridize under conditions of moderate stringency, for example, would fail to hybridize under conditions of high stringency. The metes and bounds of the claim thus cannot be ascertained. This rejection could be obviated by supplying specific conditions supported by the specification that Applicant considers to be "stringent". Applicant argues that this term is defined in the specification, however, although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim 33 recites the limitation "the peptide" in step (c). There is insufficient antecedent basis for this limitation in the claim, because in claim 1 step (a) recites "an isolated polypeptide" not a peptide. Claims 35-40, 45, 51, 53-58 are rejected insofar as they depend on claim 33.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 33, 37-38, 53-56, 58 stand rejected under 35 U.S.C. 102(b) as being anticipated by Katsura et al. (1996), for reasons of record as set forth in paper No. 10, 9/26/2003.

Katsura et al. teaches a method of testing substances for their effects on the release of soluble TNF receptor from tumor cells expressing TNF receptor. This method comprises a cell expressing TNF receptor, a substance to be tested, and a polypeptide that causes TNF receptor to be cleaved, and measurement of the soluble TNF receptor released (Katsura et al. at 299, 301). Thus claim 33 is anticipated. Katsura et al. teaches the transfection of a cell with cDNA encoding TRRE for use in the method (Katsura at 299), thus claim 37 is anticipated. Katsura et al. teaches that TRRE is a metalloprotease (Katsura at 301), thus claim 38 is anticipated. Katsura et al teaches that cell lines expressing both p55 and p75 TNF receptor were used (Katsura et al. see abstract, the THP-1 cells express both p55 and p75 TNF receptor), thus claims 53-56 are anticipated. The TNF receptor released as a result of TRRE activity was measured in culture medium (Katsura at 299), thus claim 58 is anticipated.

Applicant argues that the addition of the limitation whereby the polypeptide which cleaves TNF receptor is isolated distinguishes the claimed method from the cited reference. However, the Katsura reference sets forth a method for assaying the effect of various proteases inhibitors on TRRE function in supernatants, which can be considered an isolated form of the

protein (Katsura at 301). The assay method in which TRRE was incubated with and without inhibitors was practiced using cells expressing both p55 and p75 ((Katsura at 299), therefore the claims are anticipated.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33, 37-38, 53-58 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Katsura et al. (1996) in view of Bjornberg et al. (1995), for reasons of record as set forth in paper No. 10, 9/26/2003.

Katsura et al. teaches a method of testing substances for their effects on the release of soluble TNF receptor from tumor cells expressing TNF receptor. This method comprises a cell

expressing TNF receptor, a substance to be tested, and a polypeptide that causes TNF receptor to be cleaved, and measurement of the soluble TNF receptor released (Katsura et al. at 299, 301). Katsura et al. teaches the transfection of a cell with cDNA encoding TRRE for use in the method (Katsura at 299). Katsura et al. teaches that TRRE is a metalloprotease (Katsura at 301). Katsura et al teaches that cell lines expressing both p55 and p75 TNF receptor were used (Katsura et al. see abstract, the THP-1 cells express both p55 and p75 TNF receptor). The TNF receptor released as a result of TRRE activity was measured in culture medium (Katsura at 299).

Katsura et al. does not teach a method of testing substances for their effects on the release of soluble TNF receptor from tumor cells expressing TNF receptor wherein the binding of TNF to the surface of the cell is the indicator of TRRE activity. Bjornberg et al. teaches methods of measuring the proteolytic processing of the two TNF receptors (TNF-R55 and TNF-R75) into soluble forms in the myeloid cell lines U-937 and THP-1 (Bjornberg at 419, Table 1). Phorbol myristate acetate (PMA) rapidly stimulated release of soluble forms of both TNF-receptors. Bjornberg further teaches that 1,10-phenanthroline also reduced PMA-induced down-regulation of TNF-receptors in both cell lines as judged by TNF-binding to cells (Bjornberg at 421, Figure 2). Thus, it would have been obvious to one of skill in the art at the time the invention was made to practice a method of testing substances for their effects on the release of soluble TNF receptor from tumor cells expressing TNF receptor wherein the binding of TNF to the surface of the cell is the indicator of TRRE activity. The motivation is provided in Bjornberg et al. who teaches that PMA-induced down-regulation of TNF-binding in myeloid cells depends on metalloproteases and identification of pharmacological drugs to modulate this effect would be valuable (Bjornberg at 423).

Applicant argues that the addition of the limitation whereby the polypeptide which cleaves TNF receptor is isolated distinguishes the claimed method from the cited reference. However, the Katsura reference sets forth a method for assaying the effect of various proteases inhibitors on TRRE function in supernatants, which can be considered an isolated form of the protein (Katsura at 301). The assay method in which TRRE was incubated with and without inhibitors was practiced using cells expressing both p55 and p75 ((Katsura at 299). Thus, it would have been obvious to one of skill in the art at the time the invention was made to practice a method of testing substances for their effects on the release of soluble TNF receptor from tumor cells expressing TNF receptor wherein the binding of TNF to the surface of the cell is the indicator of TRRE activity, and wherein such activity is produced by an isolated protein.

***Conclusion***

No claim is allowed.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
August 28, 2003

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600